

REMARKS

Claims 224, 228, 232-267 and 293-294 are pending. By this Amendment, claim 224 is amended, claims 293 and 294 are added and claims 229 and 268-292 are canceled.

Reconsideration in view of the above amendment and following remarks is respectfully requested.

I. The Claims Define Patentable Subject Matter

Claims 224, 228, 229, 232-245, 248-252, 255 and 258-266 are rejected under 35 U.S.C. 103(a) as unpatentable over WO 88/05261 to Owen; claims 246 and 247 are rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of WO 96/29864; claims 253 and 254 are rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of Chambers et al.; claim 257 is rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of Ingawall or WO 97/43899; claims 259-266 are rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of U.S. Patent No. 5,586,438 to Fahy; and claim 267 is rejected under 35 U.S.C. §103(a) as unpatentable over Owen and Fahy, and further in view of Tanner et al. These rejections are respectfully traversed.

The applied art does not teach, disclose or suggest perfusing the at least one organ with a first medical fluid at a first temperature, perfusing the organ with a second medical fluid at a second temperature to at least one of maintain and restore pre-ischemia or pre-hypoxia energy levels in the organ, wherein the first temperature is from about 20°C to about 24°C.

Temperature response in tissue hypothermia is not a simple matter of metabolism getting uniformly slower as the temperature is lowered. The sensitivity of reaction rates to temperature is diverse, for example, physical processes like diffusion have a simple linear rate response to temperature. Other processes like oxygen metabolism have an exponential response to temperature. Certain enzyme and membrane mechanisms have temperature

thresholds, below which they essentially cease. Some biological macromolecules like fats have hypothermic phase transition temperatures below which they become more brittle.

The related art approach to coping with this diverse temperature response has involved preserving in two main temperature domains. A first temperature domain is cold, and just above freezing, about 4°C, where reaction rates are minimized beneficially and detrimentally. At these low temperatures, cell deterioration proceeds but at a very slow rate, and the deterioration is reversible even after many days cold storage, in some cases.

A second temperature domain is at about 37°C, which is the temperature for the device disclosed in Owen discussed below. At this temperature, all metabolic functions operate at a normal rate and so the preserved organ stays normal, as long as its supply and waste removal needs are met. However, with existing technology, the supply and waste removal requirements are so dynamic that to date a practical system has not yet been developed that thoroughly meets this need for more than 4 to 24 hours. As a consequence, preservation at this temperature has not found any clinical application.

Accordingly, applicants respectfully submit that it is significant to make targeted duration preservations at specific temperatures that allow specific metabolic results to come to pass while preventing others. An example would be the tissue pH homogeneity that is achieved at about 20°C.

As discussed on page 4 of the December 20 Office Action, the Examiner appreciates that Owen does not disclose perfusing at least one organ with a first medical fluid at a first temperature wherein the first temperature is in the range of about 20°C to about 24°C. Instead, Owen discloses the first perfusion is performed at 37°C. However, the Examiner asserts that the recited temperature range is a mere optimization of ranges and thus is considered obvious. For at least the reasons set forth above and as discussed below, applicants respectfully disagree with the Examiner's assertion.

Experiments

Kidneys for transplant that experience sustained warm ischemia (45 minutes) followed by standard hypothermic preservation methods have a higher rate of delayed function and non-function. Warm ischemia causes localized tissue acidosis, which leads to necrosis and initiation of the apoptosis cascade unless resolved. Warm ischemia also causes vascular constriction which makes it difficult for buffered perfusates to access and normalize the pH of the acidotic tissue. The experiment discussed below explores the implementation of a midthermic phase during the early stages of preservation, which has the purpose of restoring sufficient metabolism within the kidney vasculature to allow vasodilation and access of buffered perfusate to the tissue in normalization of pH.

Experiments were conducted to provide data regarding midthermia preservation of warm ischemic kidney for transplant. Again, the purpose of the experiments was to show the improved viability of warm ischemic kidneys for transplant, by adding a midthermic phase (20 to 25°C) to standard hypothermic perfusion preservation.

Experimental Procedure

1. Explant: 0 warm ischemia (control), or 45-minute warm ischemia (experiment)
2. Machine perfusion 4-8C (typical clinical) for ca. ½ hour
3. Machine perfusion at 20 to 25C for ca. ½ hour
4. Machine perfusion at 4-8C for ca. 23 hours
5. Autotransplant and contralateral nephrectomy
6. Observation and blood testing for 10-14 days

Groups:

1. MMP-45: 45 minutes warm ischemia, 24h perfusion including midthermia
2. MMP-0: No warm ischemia, 24h perfusion including midthermia
3. HMP-45: minutes warm ischemia, 24h perfusion hypothermia

Results

N	<u>MMP-45</u> 2	<u>MMP-0</u> 1	<u>HMP-45</u> 3
Survivors	2(100%)	1(100%)	2(67%)
Serum creatinine 3 days post Tx	6.25	0.8	8.2
pH at explant	6.72	7.10	n.a.
pH pre-midthermia	6.90	7.17	n.a.
pH end-midthermia	7.11	7.07	n.a.
pH hypothermia end	7.13	7.09	n.a.

Conclusions

The inclusion of a 30 minute midthermic phase is beneficial for the preservation of kidneys with 45 minutes warm ischemia. The following benefits are notable:

1. The procedure is safe, noting that all subjects survived and further noting that the midthermia control subject with 0 warm ischemia experienced full and immediate kidney function upon transplant.
2. The midthermia group had a higher rate of survival compared to hypothermia.
3. The midthermia group had lower creatinine level than the hypothermia group indicating better kidney function.
4. The midthermia process was able to reverse the locate tissue acidosis (as measured by in-tissue probes) within 30 minutes to a level comparable to the kidney without warm ischemia.

Accordingly, the results of the experiments showed that during machine preservation, a brief midthermic phase will be sufficiently metabolic to reduce warm ischemia-induced toxicity, while avoiding the potential problems associated with ex vivo normothermia.

Accordingly, applicants respectfully assert that all pending claims are patentable over Owen and the other various cited references, at least because the claimed invention provides significant and unexpected results over the references. Although Applicants submit that no prima facie case of obviousness has been established, for all of the reasons set forth above, any hypothetical prima facie case of obviousness is overcome by the demonstrated results. Those unexpected results are demonstrated in the results of the experiments represented and discussed with respect to the data set forth above.

These results further demonstrate that one of ordinary skill in the art would not have been led to the presently claimed invention from the teachings of the cited references, all of which fail to teach or suggest perfusing the organ at a first temperature of 20-24°C as in the present invention. The experimental evidence also demonstrated that the claimed invention gives substantially superior results over the prior art.

35 U.S.C. §103(a) rejection

Additionally, it is well settled that a rejection based on 35 U.S.C. §103(a) must rest on a factual basis, which the Patent and Trademark Office has the initial duty of supplying. In re GPAC, Inc., 57 F.3d 1573, 1582, 35 USPQ2d 1116, 1123 (Fed. Cir. 1995).

Several basic factual inquiries must be made in order to determine obviousness or non-obviousness of claims of a patent application under 35 U.S.C. §103. These factual inquiries are set forth in Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 467 (1966):

Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or non-obviousness of the subject matter is determined.

Graham goes on to state that:

Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

383 U.S. at 17-18, 148 USPQ at 467.

The specific factual inquiries set forth in Graham have not been considered or properly applied by the Examiner in formulating the rejection of the subject claims. Particularly, the scope and content of the prior art and the level of ordinary skill in the pertinent art were not properly determined and demonstrated and applied to the claimed invention. Moreover, the Examiner in determining the obviousness or nonobviousness of the claimed invention should properly consider the secondary considerations of nonobviousness, in the form of unexpected results.

In the present case, proper consideration of the factual inquiries demonstrates nonobviousness of the claimed invention. The cited references do not teach or suggest perfusing the at least one organ with a first medical fluid at a first temperature, perfusing the organ with a second medical fluid at a second temperature to at least one of maintain and restore pre-ischemia or pre-hypoxia energy levels in the organ, wherein the first temperature is from about 20°C to about 24°C, as claimed.

Accordingly, applicants submit that it would not have been obvious to one of ordinary skill in the art to modify the teaching of Owen. That is, the systems and methods of Owen are designed to maintain the appropriate temperature, pressure, oxygen concentration and ph of the nutrient fluid. For example, as discussed on page 20 of Owen, the acceptable ranges for temperature of perfusate for an organ are normothermic 37°C +/- 1°C and hypothermic temperature 4°C to 6°C. There are two circuits in the apparatus of Owen, one for cooling the electrolyte perfusion below 10°C and the other for maintaining the emulsion perfusion at 37°C. The electrolyte perfusion solution is cooled from refrigerant coils immersed in reservoir 4 and hydrostatic reservoir 7. Fluid passing through the circuit can also be directed

into reservoir 6 containing the emulsion perfusion, to cool the temperature of the perfusion if it exceeds 37°C. Sustaining the emulsion perfusion at 37°C is maintained by heating coils immersed in reservoir 3 and thermal regulator 5.

Thus, the apparatus of Owen is concerned with maintaining the temperatures of the fluids at "acceptable ranges". As such, Owen merely discloses perfusing at a normothermic temperature at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$. Owen does not teach, disclose or even suggest perfusing the at least one organ with a first medical fluid at a first temperature to at least one of maintain and restore pre-ischemia or pre-hypoxia energy levels in the organ, wherein the first temperature is from about 20°C to about 24°C . None of the other cited art makes up for the deficiencies of Owen discussed above.


Accordingly, applicants respectfully submit that storage of organs in a range from about 20°C to about 24°C , represents a novel and non-obvious approach to organ preservation. Withdrawal of the rejection of the claims under 35 U.S.C. §103(a) is respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



William P. Berridge
Registration No. 30,024

Kevin M. McKinley
Registration No. 43,794

WPB:KMM/jfb

Attachment:

Petition for Extension of Time

Date: May 20, 2004

OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

<p>DEPOSIT ACCOUNT USE AUTHORIZATION Please grant any extension necessary for entry; Charge any fee due to our Deposit Account No. 15-0461</p>
--